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Pharmacokinetic-Directed High-Dose Busulfan Combined with Cyclophosphamide and Etoposide Results in Predictable Drug Levels and Durable Long-Term Survival in Lymphoma Patients Undergoing Autologous Stem Cell Transplantation

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The clinical advantage of pharmacokinetic (PK)-directed–based dosing on intravenous (i.v.) versus oral busulfan-related toxicity and survival remains unclear. We performed a retrospective cohort study of sequential cohorts of patients comparing PK-directed oral and i.v. busulfan-based conditioning regimens in lymphoma patients undergoing autologous hematopoietic cell transplantation (ASCT). Patients received oral (n = 95), every 6 hours i.v. (IV16, n = 113), or once-daily i.v. (IV4, n = 86) busulfan, cyclophosphamide, and etoposide. PK-directed dosing was performed to achieve a predefined target area under the curve (AUC) of 20,000 μM-min (range: 18,400-21,600 μM-min). PK-directed dose adjustments markedly reduced the number of patients in the oral group with total AUC higher than the targeted AUC range, and reduced the variations of total AUC values in all patient groups. One hundred–day mortality was 2.1%, 3.6%, and 3.5% for oral, IV16, and IV4 cohorts, respectively. Five-year overall survival (OS) was 57% (95% confidence interval [CI] 45%-66%) and 64% (95% CI 53%-73%) for patients who received oral and i.v. busulfan, respectively. Both multivariable and instrumental variable analyses indicated the route of delivery had no significant impact on OS, whereas refractory disease and age ≥55 were significantly associated with poorer OS. In lymphoma patients undergoing ASCT, PK-directed i.v. or oral busulfan-based conditioning regimens have comparable toxicity and OS.

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INTRODUCTION

To date, there are no prospective, randomized clinical trials for determining the optimal conditioning regimens for hematopoietic stem cell transplantation (HSCT). Studies examining the role of busulfan in high-intensity conditioning regimens provide retrospective comparisons of the toxicity of oral versus intravenous (i.v.) busulfan administration, with limited information regarding the efficiency of pharmacokinetic (PK)-directed busulfan dosing in the setting of autologous HSCT. Comparisons of overall survival (OS) between i.v. and oral busulfan have not been performed when PK-directed dosing is applied in both contexts [1]. In addition, daily i.v. administration of busulfan via PK-directed dosing may offer convenience over 4 times daily dosing with highly predictable pharmacokinetics [2]. However, the efficacy of this regimen has not been well studied in comparison to alternative busulfan dosing regimens.

In addition to the clinical considerations above, HSCT remains a highly costly procedure [3], which justifies the need for economic evaluation of factors that impact HSCT. Multiple reports have highlighted the importance of initial hospital stay in the total cost

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of HSCT [4] and the advantages of limiting the duration of neutropenia and shortening the length of hospital stay [5] as strategies to reduce costs. With respect to the conditioning regimen, the cost of i.v. busulfan constitutes a significant incremental expense compared with oral delivery, which should be counterbalanced by reduced toxicity and/or improved efficacy [1]. We hypothesized that i.v. administration of busulfan with a targeted area under the curve (AUC) of 20,000 μM-min (range: 18,400-21,600 μM-min) may provide improved efficiency in achieving the target AUC level with safety and efficacy comparable to oral busulfan, and designed a retrospective cohort study to perform this comparison.

MATERIALS AND METHODS

Design

This retrospective, observational cohort was conducted with a preexisting database populated with Hodgkin's lymphoma (HL) and non-Hodgkin lymphoma (NHL) patients undergoing their first autologous stem cell transplantation (ASCT) at Emory Hospital between July 20, 1999, and May 19, 2010 (n = 294). In May 2004, our program changed the standard of care from oral to i.v. busulfan. The Emory institutional review board approved use of patient data for this analysis. Patients received either oral (1 mg/kg every 6 hours × 4 days from day −8 to day −5, n = 95) or IV16 (0.9 mg/kg every 6 hours for 16 doses from day −8 to day −5, n = 113), or IV4 (3.6 mg/kg daily × 4 from day −8 to day −5, n = 86), followed by cyclophosphamide (Cy, 60 mg/kg every day × 2 on days −3 and −2) and, etoposide (E, 10 mg/kg every day ×3 on day −4 to day −2). Busulfan was dosed using ideal body weight if the ratio of total body weight to ideal body weight ratio was ≤1.3; otherwise, busulfan was dosed according to an adjusted body weight, calculated as the ideal weight plus 25% of the difference of total and ideal weights. For patients weighing less than ideal body weight, busulfan was dosed on total body. E and Cy were based upon an average of ideal and actual body weight for patients whose weight exceeded their ideal body weight by a factor of 1.3 or greater, and actual body weight for patients whose weight was <1.3 × their ideal body weight. Following oral busulfan administration, half or full doses were readministered if vomiting occurred < or >60 minutes following any single dose, respectively. Following 1 day of no chemotherapy (day −1), patients received infusion of autologous bone marrow cells or granulocyte colony-stimulating factor–mobilized peripheral blood stem cells that had been previously collected, frozen, and thawed immediately before infusion as previously reported [6]. A minimum dose of 2×10^6 $CD34^+$ cells/kg was required for transplantation. Severe hepatic veno-occlusive disease (HVOD) was diagnosed based on Baltimore criteria [7].

PK-Directed Dosing

In this study, following the initial i.v. or oral dose, PK monitoring of busulfan plasma levels was accomplished using the high-performance liquid chromatography method with mass spectrometry by Department of Pathology and Laboratory Medicine at Emory University School of Medicine and Emory Healthcare Systems. The predicted total AUC was calculated by extrapolating the AUC derived from PK analysis of the first dose of busulfan. Before 2003, PK-directed dosing modifications were applied only to patients with predicted total AUC >24,000 μM-min. Since 2003, all patient doses were adjusted to deliver an average total AUC of 20,000 μM-min (range: 18,400-21,600 μM-min). The busulfan AUC and elimination half-life were calculated using a combination of linear and logarithmic trapezoidal rules as described by Grochow [8]. The AUC during infusion was calculated using the linear rule, and the postinfusion AUC was calculated using the logarithmic rule. For first dose levels, the AUC from the last concentration to infinity was calculated using the elimination rate constant determined by regression of the log-transformed levels of the elimination phase.

Statistical Methods

The median value of the continuous variables was used as a cutoff point for exploratory analysis. Categoric variables including sex, race, diagnosis, and disease status at transplantation were compared by regimens and route of administration using chi-square tests. Disease status at transplantation was classified into 4 categories based on treatment response according to the definition by the American Society for Bone Marrow Transplantation and Center for International Blood and Marrow Transplant Research. They are complete remission (CR)1 or CRu1 (CR1 with the exception of persistent scan abnormalities of unknown significance) as category I; CR2 or CRu2 as category II; PR (partial remission)1, PR2, or CR3 as category III; and refractory disease as category IV. The 100-day transplant-related mortality was defined as death within 100 days posttransplantation without relapse or disease progression. OS was defined as the time from transplantation to last follow-up or death irrespective of the cause of death. Probabilities of OS were calculated using the Kaplan-Meier estimate; the log-rank test was used for univariate comparisons. Association of patients' characteristics with outcomes was evaluated with stepwise Cox proportional hazards regression models. Hazard ratios (HR) are presented with a 95% confidence interval (CI). Factors associated with a *P* value

Table 1. Route of Busulfan Delivery by Year of Transplantation (n = 294)

	1999-2001	2002-2004	2005-2006	2007-2008	2009-2010	Total
Oral	34	61	0	0	0	95
IV16	0	21	74	18	0	113
IV4	0	0	0	38	48	86

<.10 by univariate analysis and factors with a priori clinical relevance were included in the final model. All tests were 2 sided, with $\alpha = 0.05$ for determination of statistical significance. Multiple comparison corrections were conducted with the Bonferroni adjustment. Statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

To reduce the bias in this retrospective study because of adoption of new supportive care and treatment protocols, an instrumental variable analysis was applied under the 2 key assumptions: the instrument should have statistically significant impact on the route of administration; and the instrument should not be associated with overall survival [9-11]. The analysis took a 2-stage estimation approach, that is, the first stage predicts the instrument and other baseline factors, and the second-stage estimates the effect of the route on OS incorporating the "instrumental variable" derived from the first-stage estimation using a Cox regression model [12].

RESULTS

Patient Characteristics

The route of busulfan administration differed by year of transplantation, with each regimen occurring in serial cohorts of patients (Table 1). The median ages for patients receiving oral, IV16, and IV4 regimens were 45, 47, and 47 years, respectively. Patients' median age, race, lymphoma diagnosis, body surface area, and $CD34^+$ cell count were comparable across the regimens except that patients receiving IV16 busulfan dosing had a significantly higher body weight index than the other 2 groups (Table 2). In addition, the distribution of disease status at transplantation was different across 3 regimens with a greater proportion of patients with advanced disease status (category III) receiving IV busulfan and with refractory disease status (category IV) receiving oral busulfan, respectively. The majority of patients received peripheral blood stem cells. Because treatment strategies were utilized in a serial fashion, patients treated with oral busulfan had significantly longer follow-up than those receiving IV16 and IV4 busulfan.

Toxicity

Among patients who had an elevated maximum bilirubin (≥2 mg) within the first 30 days posttransplantation (oral group: n = 13, 14%; IV group: n = 38, 19%), none developed severe HVOD by Baltimore criteria. Grade 3-4 neurotoxicities were not observed in any patients. There was no difference in the length of hospital stay among 3 regimens. However, average hospital stay was significantly longer for female patients (23.8 ± 4.3 days) than male patients (22.5 ± 3.4, $P = .0159$), and for African-American (AA) patients (AA, 24.3 ± 4.8) than non-AA (22.7 ± 3.5, $P = .0071$).

Outcomes

The frequency of early death, occurring within the first 100 days posttransplantation was not different for patients receiving oral busulfan (2 deaths, 2.1%), IV16 (4 deaths, 3.5%), or IV4 (3 deaths, 3.5%, $P = .512$). One-year and 2-year OS were comparable regardless of the route of busulfan delivery or dosing regimen. One-year OS for oral busulfan was 88.3% (95% CI 79.9-93.3), for IV16 was 80.3% (95% CI 71.1-86.8), and for IV4 was 80.1% (95% CI 67.7-88.1). Two-year OS for oral busulfan was 72.7% (95% CI 62.3-80.6), and was 71.2% for IV16 dosing (95% CI 60.9-79.2). Estimated 5-year OS for patients receiving i.v. busulfan (combining IV16 and IV4 cohorts) showed a trend toward better OS among recipients of i.v. busulfan compared with that for patients receiving oral busulfan (63.9%, 95% CI 52.7-73.1 versus 56.5%, 95% CI 45.3-66.3, respectively, $P = .10$).

As the group receiving once-daily busulfan (IV4) had relatively short median follow-up, both univariate and multivariate analysis were performed comparing the 2 groups receiving oral versus i.v. busulfan (combing IV16 and IV4) groups. Univariate analysis revealed (Table 3) that age ≥55 years (HR = 1.64, 95% CI 1.09-2.49) and refractory disease at the time of relapse (HR = 1.65, 95% CI 1.04-2.61), but not the route of busulfan administration, were significantly associated with OS (Figure 1). In addition, patients with a diagnosis of HL or patients with Karnofsky performance status (KPS) >80 tended to have better OS than patients with a diagnosis of NHL (HR = 0.69, 95% CI 0.45-1.06) or patients with lower KPS (HR = 0.67, 95% CI 0.44-1.02), respectively. Importantly, the change in practice of PK-directed dosing, that is, changing doses for AUC of >24,000 μM-min (before 2003) versus changing doses for AUC outside of the target range of 18,400-21,600 μM-min (after 2003) did not have an impact on OS as indicated by log-rank testing. The number of $CD34^+$ cells transplanted (less or greater than the median value 7×10^6/kg), sex, and race also had no impact on OS.

Consistent with univariate analyses, a multivariable Cox proportional hazards regression model (Table 3) showed that route of busulfan administration had no effect on the OS, whereas age ≥55 (HR = 1.67, 95% CI 1.09-2.56) and refractory disease status at transplantation (HR = 1.84, 95% CI 1.15-2.93) were

Table 2. Characteristics of the Transplanted Patients and Main Clinical Findings (Average with Minimum and Maximum)

	Oral (n = 95)	IV16 (n = 113)	IV4 (n = 86)	*P* value*
Median age (years)	45 (19-66)	47 (17-69)	47 (18-66)	.4105
>55	25 (26%)	35 (31%)	28 (33%)	.406
Male/female	64/31	73/40	50/36	.412
Race				.064
White, n = 215	73	87	55	
African American (AA), n = 56	18	21	17	
Asian, Hispanic, other, n = 17	3	4	10	
BSA	1.96 (1.56-2.60)	2.03 (1.44-2.84)	2.00 (1.58-2.53)	.1242
Body mass index (kg/m^2)	27.50 (17.86-53.63)	30.23 (17.41-62.65)	28.51 (18.41-45.30)	.01
Diagnosis				.713
HL, n = 122	43	44	35	
NHL, n = 172	52	69	51	
Disease status at transplantation				<.0001
I: CR1/CR$_U$1, n = 45	10 (11%)	17 (15%)	18 (21%)	
II: CR2/CR$_U$2, n = 65	27 (28%)	25 (22%)	13 (15%)	
III: PR1/PR2/CR3, n = 127	29 (30%)	47 (41%)	51 (59%)	
IV: Primary refractory, n = 53	25 (26%)	24 (21%)	4 (5%)	
Median CD34$^+$ count ($\times 10^6$/kg bodyweight), n = 263	5.62 (1.66-95.94), n = 80	6.95 (2.98-68.25), n = 106	6.47 (2.21-135.35), n = 77	.3035
Source: PBSC†	95	113	86	
Median KPS, n = 273	80 (70-100), n = 76	80 (70-100), n = 111	90 (60-100), n = 86	.003
Median length of hospitalization (days)	22.0 (2-42), n = 74	22.0 (9-48), n = 99	22.0 (12-43), n = 85	<.01
Median follow-up (days)	1565 (10-4184)	929 (12-3311)	311 (33-845)	<.0001
Maximum bilirubin by day 30	1.58 (0.5-22.4)	1.62 (0.6-10.4)	2.06 (0.6-10.6)	.2144

BSA indicates body surface area; PBSC, peripheral blood stem cell.

*P value denotes the effect of conditioning regimen.

†There were 5, 2, and 1 patients receiving PBSC plus CD34$^+$ in the oral, IV1, and IV4 groups, correspondingly. There were 2 patients receiving PBSC plus bone marrow and 1 patient receiving bone marrow only in the oral group.

independent predictors of poor survival in this cohort. Multivariate analysis revealed moderate association of KPS >80 with reduced risk of mortality (HR = 0.68, 95% CI 0.45-1.05). There was no interaction between the route of administration with either disease status or diagnosis. Despite differences in KPS for patients in the oral, IV16, and IV4 groups (eg, percentage with KPS >80 was 35%, 48%, and 74%, respectively, $P < .0001$), there was no significant interaction between KPS and route of busulfan administration in the regression model. Because i.v. busulfan had gradually replaced oral busulfan among patients treated after 2002, we examined whether the year of transplantation could be an instrumental variable affecting the choice of treatment. Transplantation year was significantly associated with the administration route ($R^2 = .637$, $P < .0001$) but not with other baseline factors, including sex, body mass index, diagnosis, age, race, and disease status at relapse, and had no impact on OS. A 2-stage instrumental variable analysis confirmed the findings by the multivariate analysis that age ≥55 (HR = 1.87, 95% CI 1.13-3.08), refractory disease status at transplantation (HR = 1.75, 95% CI 1.02-2.99), and KPS >80 (HR = 0.48, 95% CI 0.26-0.88), but not route of administration (HR = 1.60, 95% CI 0.89-2.84), had significant effects on OS. Female patients also had significantly worse OS than male patients (HR = 1.88, 95% CI 1.15-3.08).

Pharmacokinetics

At the initial dose, 5 patients in the oral group missed PK assessment because of vomiting, whereas none of the patients in the IV groups missed PK assessments, and 4 patients in the oral group were switched to the IV16, group because of inability to take oral busulfan. By design, IV4 dosing resulted in significantly higher initial AUC than the other 2 groups ($P < .0001$). The half-life of busulfan following oral administration was significantly longer than that after i.v. administration (Table 4, $P = .001$). Oral administrations resulted in a significantly wider range of total AUC than both the IV4 and IV16 groups ($P = .0003$; Figure 2A). More than one-quarter of patients receiving i.v. busulfan had an initial total predicted AUC within the target range (IV16 29%, IV4 28%), whereas only 18% of patients receiving oral busulfan had an initial total predicted AUC within the target range of 18,400-21,600 μMol-min. In addition, the majority of patients receiving oral busulfan (60%) had an initial total predicted AUC above the targeted range, whereas this only occurred in 19% of the IV16 group and in 30% of the IV4 group (Figure 2A).

Regardless of dosing regimens, the majority of patients (72%) had dose adjustments, and 109 patients had repeated PK sampling (52%). When repeated PK assessment was performed, the total predicted AUC (for all doses) was not different comparing among the IV groups, but a wide range of variation remained in the oral group despite a similar mean AUC value to those in the IV groups. The majority of patients receiving IV16 (81%) and IV4 (82%) busulfan had total predicted AUC values in the target range, while 43% of patients who received oral busulfan had total predicted AUC values in the target range ($P < .0001$), and 39%

Table 3. Univariate and Multivariate Analysis of Prognostic Factors for Overall Survival

	Univariate		Multivariate		Instrumental Variable Analysis	
Variable*	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
BMT year: per 1-year increase	1.06 (0.98-1.14)	.152	—	—	—	—
After 2003 versus before 2003	1.10 (0.71-1. 76)	.629				
Route: i.v. versus oral	1.06 (0.69-1.62)	.781	1.12 (0.73-1.71)	0.611	1.60 (0.89-2.84)	.114
Age: ≥55 versus <55	1.64 (1.09-2.49)	.019	1. 67 (1.09-2.56)	0.018	1.87 (1.13-3.08)	.014
Per 10-year increase	1.22 (1.06-1.44)	.005				
Disease status at relapse: increase in per category	1.24 (1.01-1.56)	.054				
III+IV versus I+II	1.50 (0.97-2.30)	.065				
Refractory versus chemosensitive disease	1.65 (1.04-2.61)	.032	1.84 (1.15-2.93)	0.010	1.75 (1.02-2.99)	.041
KPS: >80 versus ≤80	0.67 (0.44-1.02)	.065	0.68 (0.45-1.05)	0.084	0.48 (0.26-0.88)	.018
Sex: female versus male	1.16 (0.77-1.77)	.473	—	—	1.88 (1.15-3.08)	.012
Diagnosis: HL versus NHL	0.69 (0.45-1.06)	.091	—	—	—	—
Race: AA versus non-AA	1.48 (0.91-2.40)	.118	—	—	—	—
$CD34^+ \times 10^6$/kg: ≥ median value 7 versus <7	0.81 (0.54-1.21)	.305	—	—	—	—

*Within each variable, the reference for the analysis: BMT year before 2003, route with oral, age <55, chemosensitive disease at transplantation, KPS ≤80, male, NHL, non-AA, CD34+ $\times 10^6$/kg with median value <7.

of the patients receiving oral busulfan had total predicted AUC values greater than the target range (Figure 2B, Table 4).

The initial total predicted AUC was not correlated with race, age, sex, diagnosis, disease status, transplantation year, and performance status, but was significantly associated with the busulfan plasma half-life $T_{1/2}$ ($r = .2774$, $P < .05$). The total predicted AUC recalculated following the dose adjustment was not affected by these baseline variables.

DISCUSSION

The current study reveals that lymphoma patients undergoing ASCT after conditioning with a PK-redirected high-dose busulfan, cyclophosphamide, and etoposide (BuCyE) regimen had equivalent OS irrespective of the route of busulfan administration, with no significant differences seen in the incidence of severe HVOD or 100-day mortality comparing oral versus intravenous administration. Our report is largely comparable to previously reported series using other similar busulfan-based regimens [13,14]. Consistent with previous reports [15,16], oral administration of busulfan resulted in a longer serum half-life and wider variation in AUC, with 43% of patients receiving oral busulfan having a total predicted AUC within the target range, whereas more than 82% of patients receiving i.v. busulfan had a calculated total predicted AUC in the target range following PK-directed dose adjustments. These differences between oral and i.v. dosing cohorts are partly because of practice changes in dose adjustments, because many patients with low AUC values receiving oral busulfan did not have dose adjustments (increases) in contrast to more recently treated patients in the i.v. cohorts in which all patients with total predicted AUC above or below the target range had dose adjustments. However, 39% of the patients receiving oral busulfan continued to have total predicted AUC greater than the target range following initial dose adjustments, suggesting that the i.v. route may produce some efficiency in achieving the target AUC. Overall this series indicates that careful monitoring of drug levels following both oral and i.v. busulfan administration can avoid extremely high cumulative drug levels, decreasing the fraction of all patients with total predicted AUC above the target range from 35% (before dose adjustments) to 19% (after PK-directed dose adjustments). Of note, only 6% of the recipients of i.v. busulfan had

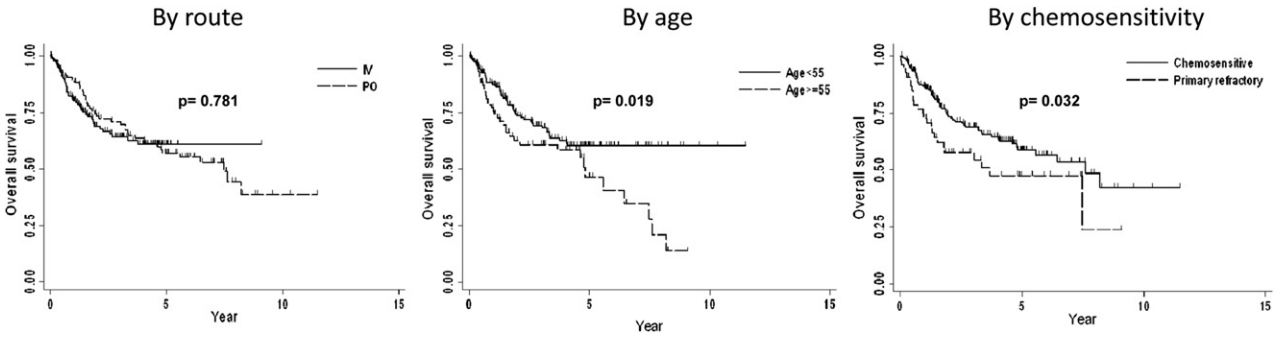

Figure 1. Univariate analysis of prognostic factors on overall survival. The Kaplan-Meier method was used to estimate overall survival for patients receiving autotransplants for NHL or HL after conditioning with BuCyE. Patients were stratified by route of administration (i.v. versus oral), age at transplantation (age ≥ 55 versus younger), and chemosensitivity at transplantation (primary refractory versus chemosensitive disease in PR or CR). *P* values were derived from the log-rank test.

Table 4. Pharmacokinetic Characteristics

	Oral	IV16	IV4
All patients	n = 95	n = 113	n = 86
Starting dose (mg; mean ± SD)	65.6 ± 6.4	63.3 ± 10.6*	254.3 ± 40.2†
$T_{1/2}$ (minutes; mean ± SD)	222.6 ± 104.3	190.1 ± 58.4†	188.5 ± 26.2†
Initial total predicted AUC (μM-min; mean ± SD)‡	22,379 ± 5288 (n = 78)	18,607 ± 3499† (n = 103)	20,228 ± 4737† (n = 84)
% at targeted AUC	18% (n = 14)	29% (n = 30)†	28% (n = 24)†
% above targeted AUC	60% (n = 47)	19% (n = 20)†	30% (n = 25)†
% below targeted AUC	22% (n = 17)	52% (n = 53)†	42% (n = 35)†
% patients with dose adjustments	80% (n = 75)	66% (n = 75)	71% (n = 61)
Adjusted dose (mg; mean ± SD)	61.2 ± 15.6	67.7 ± 16.0	253.5 ± 91.0†
$T_{1/2}$ (minutes; mean ± SD)	234.6 ± 73.7	198.4 ± 40.1†	194.1 ± 35.0†
Total predicted AUC after dose adjustment (μM-min; mean ± SD)	20,584 ± 3005	19,431 ± 1313†	20,201 ± 1557
% at targeted AUC§	43% (n = 32)	81% (n = 61)†	82% (n = 50)†
% above targeted AUC	39% (n = 29)	4% (n = 3)†	15% (n = 9)†
% below targeted AUC	19% (n = 14)	15% (n = 11)	3% (n = 2)†

*The first 16 patients treated with IV16 dosing received 0.8 mg/kg every 6 hours; the dose was increased to 0.9 mg/kg every 6 hours for the subsequent 97 patients, following an analysis that showed 65% of the AUC values were below and only 26% of the AUC values were within the target range.
†Comparison of either IV16 or IV4 with oral group with significance level $P < .05$.
‡The number of patients with initial total AUC (n = 265) was used as the denominator for the percentage calculation. Patients who received multiple dose adjustments were only counted once.
§Percentage was calculated with the patients receiving dose adjustments (total of 211) as the denominator for each group.

high total predicted AUC. Furthermore, the approach utilizing PK-directed dose adjustments dramatically reduced the range of variation in total predicted AUC among all conditioning regimen groups compared with those values in the initial total predicted AUC (Table 4). The low fraction of patients with high total predicted AUC may have contributed to the low 100-day mortality and absence of severe HVOD reported in this single institution experience.

A limitation of this study is that it is retrospective and limited to transplant patients who were treated at a single institution. Because the study spanned a 11-year period, the data on the time of relapse was incomplete, especially for patients who had returned to the care of their initial oncologist. Because >80% of deaths among transplant recipients were because of disease progression, OS most appropriately represents disease control in this series. Other limitations of this study include the modest sample size and practice-based protocols for PK-directed dosing. Additionally, the lack of complete data on some of the important prognostic factors, such as treatment history and comorbidity scores, and the key outcome measures, such as response duration, limit the analysis of the comparative effectiveness of the BuCyE regimens studied.

The 1-year and 5-year survival for the IV groups (combining IV16 and IV4) in this series are remarkably similar to what has been reported in previous studies of busulfan-based [13,14,17] and nonbusulfan-based conditioning regimens [18] for lymphoma patients undergoing ASCT. The current study had sufficient patients in the once-daily dosing IV4 group (n = 86) to conclude that these patients have similar 100-day mortality and 1-year OS to those receiving every 6-hour i.v. dosing, similar to the conclusions of a randomized study of PK-directed IV4 versus IV16 conditioning regimens (n = 30/group) [19]. Our reported 5-year OS in the cohort of patients receiving oral busulfan is consistent with a previous report in HL patients with a median age of 33 [20], and is corroborated by a recent study using the United States Surveillance, Epidemiology, and End Results data for patients with diffuse large B-cell lymphoma [21]. A phase II clinical trial currently being pursued is assessing the toxicity and efficacy of PK-directed once-daily i.v. administration of busulfan in combination with cyclophosphamide and etoposide compared with a matched

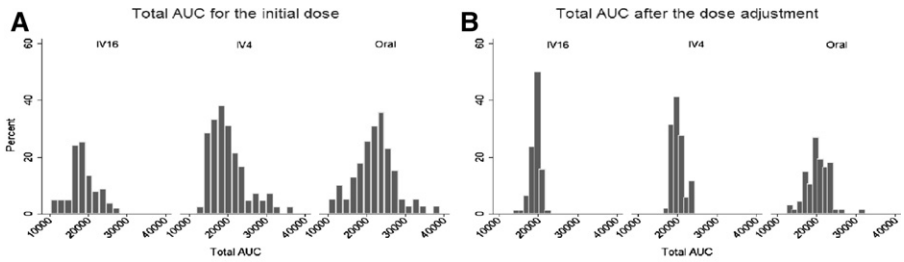

Figure 2. Histograms of total predicted AUC based on dosing regimen. (A) Histograms of total predicted busulfan AUC following the initial dose among patients treated with the IV16 (n = 113), IV4 (n = 86), and oral (n = 95) regimens. (B) Histograms of total predicted AUC following PK-directed dose adjustment among patients treated with the IV16 (n = 75), IV4 (n = 61), and oral (n = 75) regimens.

control group of contemporaneous patients treated with carmustine, etoposide, cytarabine, and melphalan (BEAM) regimen. This prospective, multicenter study will help determine if our single-institution results from PK-directed dosing can be reproduced.

However, in contrast with previous reports, the present study has shown comparable efficacy and toxicity between regimens utilizing oral and i.v. delivery of busulfan. This could be because of several reasons: (1) PK-directed dosing adjustment may overcome the greater interpatient variation in busulfan AUC seen in patients receiving an oral drug; (2) the use of a conservative AUC target and narrow AUC target range of 20,000 ± 1600 μMol-min; (3) a lower median age of patients in the current series (47 years) compared with the reported studies [13,14,17]. In particular, other published series have utilized a broader target AUC (16,000-24,000), with a lower percentage of patients receiving PK-directed dose adjustment.

The effect of race and ethnicity on PK profiles and efficacy has been largely understudied in cancer drugs [22], and the limited numbers of minority patients undergoing HSCT [23] has made it difficult to use ethnicity as a covariate in prognostic models. The unusually high percentage of AA in this study population (19%) reflects the high AA population in the state of Georgia (31% of the population), which is significantly greater than the national average (12.6%) based on the 2010 U.S. Census Bureau report (http://2010.census.gov/2010census/data/). The current study found that AA patients and the female patient group had a longer hospitalization, but this disparity was not reflected in differences in OS. Nevertheless, our study indicates very similar clinical outcomes and pharmacokinetics parameters for AA lymphoma patients versus non-AA lymphoma patients undergoing high-dose busulfan-based conditioning and autologous HSCT.

Although the current study did not include a pharmaco-economic analysis, the equivalent survival and similar lengths of hospitalization comparing recipients of oral and i.v. busulfan formulations make it unlikely that a formal cost-effectiveness comparison would favor i.v. busulfan. Although the overall cost of i.v. busulfan regimens can be reduced if PK-directed dose adjustments are eliminated, a substantial fraction of patients receiving i.v. busulfan in this series (68%) had dose-adjustments following PK measurements. It is unknown if outcomes for patients receiving i.v. busulfan with total predicted AUC above or below the target range (without PK-directed dose adjustments) would be similar to the outcomes measurements reported herein. Alternatively, once-daily i.v. delivery of busulfan with PK monitoring could be potentially cost-effective if fewer dose adjustments are required compared with the administration of oral busulfan. In light of the higher cost of the i.v. formulation, a larger, prospective study would be needed to determine if the reduced need for repeated PK monitoring in the administration of i.v. busulfan and the slight improvement in OS by i.v. over the oral busulfan-based regimen we observed in the present study would justify the added expense.

In conclusion, PK-directed i.v. and oral delivery of busulfan resulted in total predicted AUC largely within a well-defined targeted range for lymphoma patients undergoing autologous ASCT. Because patients that received PK-directed i.v. and oral busulfan had similar toxicity and OS, either route can be utilized when PK-directed dose adjustments are being performed to optimize busulfan dosing. Future studies are needed to determine whether the improvement in OS identified in this study for i.v. over oral PK-directed busulfan-dosing is present in other settings.

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